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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,418	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	EMILY M. LE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/04/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11 and 39* is/are pending in the application.

4a) Of the above claim(s) *39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-8, 10 and 12-38 are cancelled. Claim 39 was added. However, claim 39 is not in accordance with Applicant's election of Y, as a Y is a non-natural pyrimidine nucleoside. Thus, the claim has been withdrawn from examination. Therefore, claims 9 and 11 are under examination.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al.,[1] as evidenced by Peyrottes et al.[2]

In response to the rejection, Applicant argues that Schwartz et al. does not teach or suggest the limitation that at least one of X1, X2, X3 or X4 is one of the specifically recited immunostimulatory moieties for each position, which Applicant has demonstrated through structure activity relationship (SAR) studies, to determine precisely which chemical groups at precisely which position within the immunostimulatory domain would achieve the result of rendering the oligonucleotide more immunostimulatory than its non-immunostimulatory moiety including equivalent.

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[1] Schwartz et al. WO 99/62923, published December 9, 1999.
[2] Peyrottes et al. Oligodeoxynucleoside phosphoramidates (P-NH_2): synthesis and thermal stability of duplexes with DNA and RNA targets. Nucleic Acids Research, 1996, Vol. 24, No. 10, 1841-1848.

Applicant cites lines 23-26 of page 13 and Table 1, page 15 of the specification to evidence/support this teaching. Applicant also submits that Applicant has demonstrated that the insertion of immunostimulatory moiety suggested by Schwartz et al. at the X1 or X2 position does not act as an immunostimulatory moiety, as defined in the specification. Applicant submits this latter point to demonstrate a lack of a reasonable expectation of success.

Applicant's argument has been considered, however, it is not found persuasive. *KSR* forecloses the argument that specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR*, 82 USPQ2d at 1396. Schwartz et al. does not need to teach the specific immunostimulatory moiety at a specific location to render the claim invention obvious for it would have been prima facie obvious for one of ordinary skill in the art to insert an immunostimulatory moiety into the CpG containing oligonucleotide of Schwartz et al. because Schwartz et al. suggests the insertion of an immunostimulatory moiety into CpG oligonucleotides to increase the stability of the oligonucleotide, as detailed in the rejection. While Schwartz et al. does not teach or suggest the insertion of the specific immunostimulatory moiety at a specific location, however, it would have been prima facie obvious for one of ordinary skill in the art to insert the moiety suggested by Schwartz at various location, including those being claimed by Applicant to stabilize the oligonucleotide as part of routine experimentation.

Additionally, it should be noted that the entire disclosure, including Table 1 of page 15 and lines 23-26 of page 13 have been considered. Table 1 contains the limitation of the claims, wherein X is of a particular position and immunostimulatory

moiety flanking the CpG motif. Lines 23-26, page 13 of the disclosure provides a definition of "immunostimulatory moiety" as "a chemical structure at a particular position within the immunostimulatory domain or the potentiation domain that causes the immunostimulatory oligonucleotide to be more immunostimulatory than it would be in the absence of the immunostimulatory moiety". However, it is found that the results obtained by Applicant are predicted by Schwartz et al., who clearly teaches the insertion of immunostimulatory moiety to increase the stability of the oligonucleotide. It is further noted that the specification teaches that the "precise" chemical groups at the "precise" position do not render any unexpected results. This is evidenced by Figure 13. Figure 13 demonstrates that the "precise" chemical groups at the "precise" position as claimed do not yield unexpected results. Moreover, it should be noted that Applicant's finding is limited to one oligonucleotide, those having the sequence of Oligo No. 131-1, and is not representative of all immunostimulatory oligonucleotides.

Regarding Applicant's submission that the insertion of immunostimulatory moiety suggested by Schwartz et al. at the X1 or X2 position does not act as an immunostimulatory moiety, as defined in the specification, it should be noted that neither does the insertion of the moiety at the X3 position. Figure 13 shows that the insertion of methylphosphonate at the X3 position does not enhance the immunostimulatory activity of the test oligonucleotide.

Applicant's argument of lack of reasonable expectation of success has been considered, however, it is not found persuasive. Applicant is reminded that the standard is "reasonable expectation of success", not absolute prediction of success. As

mentioned, while Schwartz et al. does not teach or suggest the insertion of the specific immunostimulatory moiety at a specific location, however, it would have been prima facie obvious for one of ordinary skill in the art to insert the moiety suggested by Schwartz at various location, including those being claimed by Applicant to stabilize the oligonucleotide as part of routine experimentation.

The claims are directed to an oligonucleotide having the formula X1X2CGX3X4, wherein X1-X4 are a nucleoside each or a immunostimulatory moiety, wherein the immunostimulatory moiety for X1 is limited to one selected from a group consisting of C3-alkyl linker, 2-aminobutyl-1,3-propanediol linker and Beta-L-deoxynucleoside; for X2 is an amino linker; for X3 is a methylphosphonate; for X4 is methylphosphonate; and wherein C is a non-natural pyrimidine nucleoside, and G is guanosine, 2'deoxyguanosine or a non-natural purine nucleoside. Claim 11, which depends on claim 9, requires the non-natural pyrimidine nucleoside to have the formula set forth in the claim, formula (I).

Schwartz et al. teaches of immunostimulatory oligonucleotides having the formula X1X2CGX3X4, wherein X1-X4 are a nucleoside each; and wherein C is a non-natural pyrimidine nucleoside, and G is 2'deoxyguanosine. [Table 1, page 35, in particular.] It is noted that the oligonucleotides of Schwartz et al. does not have a non-natural pyrimidine set forth in formula (I). However, it is further noted that Schwartz et al. does suggest the use cytosine arabinoside, a non-natural pyrimidine nucleoside. [Claim 4, page 39 in particular.] Cytosine arabinoside is in accordance with formula (I).

Hence, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to use cytosine arabinoside as an alternative to the other non-natural pyrimidines present in the oligonucleotides of Schwartz et al. One of ordinary skill in the art, at the time the invention was made would have been motivated to do so to make an immunostimulatory oligonucleotide. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the substitution of equivalents is routinely practiced in the art.

Regarding the limitation that at least one of X1-X4 is an immunostimulatory moiety instead of being a nucleoside each, wherein the immunostimulatory moiety is defined is a nucleoside methylphosphonate, it is noted that Schwartz et al. teaches that the nucleosides present in the immunostimulatory oligonucleotide may comprise a modified backbone, Wherein instead of the naturally occurring phosphodiester backbone that allows linkage between nucleosides can be substituted with other phosphorous backbone derivatives to increase the stability of the oligonucleotide. Of the derivatives that Schwartz et al. teach include alkylphoshate or the like, which methylphosphate is the most basic alkylphosphate. Addition to suggesting alkylphosphate, Schwartz et al. also referred to the teachings of Peyrottes et al., which teaches the use of methylphosphonate to stabilize oligonucleotides. Hence, in the instant case, Schwartz et al. suggests the use of methylphosphonate as an alternative to the natural phosphodiester backbone that links nucleosides.

Thus, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to modify the backbone of at least one X1-X4 of Schwartz et al. to render it as a nucleoside methylphosphonate. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to stabilize the oligonucleotide. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the substitution of one nucleoside linkage for another is routinely practiced in the art.

4. Claims 9 and 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nguyen et al.,[3] in view of Schwartz et al.

In response to the rejection, Applicant submits the same arguments as those addressed in paragraph No. 4 of the instant application. These arguments have been considered and found not persuasive for the reason(s) set forth in the cited paragraph.

Applicant also criticized the Office's inherent position. Applicant argues that the correct standard for evaluating allegedly inherent feature of a prior art compound in an obvious analysis is whether the inherency of the feature was itself known or obvious at the Applicant's filing date.

Applicant's argument has been considered, however it is not found persuasive. Nguyen et al. teaches an oligonucleotide that comprises the CpG motif. The oligonucleotide of Nguyen et al. inherently has immunostimulatory activity, for at the time of Applicant's filing date, Schwartz et al. evidences that the presence of CpG motif in an oligonucleotide renders the oligonucleotide immunostimulatory. Schwartz et al.

also evidences that it is prima facie obvious for one of ordinary skill in the art to include an immunostimulatory moiety to the CpG oligonucleotide to increase the stability of the oligonucleotide.

Nguyen et al. teaches several oligonucleotides having the formula X1X2CGX3X4, wherein X1-X4 are a nucleoside each. The C in the oligonucleotides of Nguyen et al. is N4-ethylcytosine, a non-natural pyrimidine nucleoside, and G is 2'deoxyguanosine. [First full paragraph, left column on page 3061; Figure 2, and Tables 1-3, in particular.] N4-ethylcytosine is not a cytidine or deoxycytidine, and have a formula that is in accordance with formula (I), wherein D a hydrogen bond donor, D' is a hydrogen, A is a hydrogen bond acceptor, S is a pentose sugar ring, and X is nitrogen.

Regarding the limitation that at least one of X1-X4 is an immunostimulatory moiety instead of being a nucleoside each, wherein the immunostimulatory moiety is defined is a nucleoside methylphosphonate, it is noted that Schwartz et al. teaches that the nucleosides present in immunostimulatory oligonucleotides may comprise a modified backbone, Wherein instead of the naturally occurring phosphodiester backbone that allows linkage between nucleosides can be substituted with other phosphorous backbone derivatives to increase the stability of the oligonucleotide. Of the derivatives that Schwartz et al. teach include alkylphoshate or the like, which methylphosphate is the most basic alkylphosphate. Addition to suggesting alkylphosphate, Schwartz et al. also referred to the teachings of Peyrottes et al., which teaches the use of methylphosphonate to stabilize oligonucleotides. Hence, in the

[3] Nguyen et al. Modification of DNA duplexes to smooth their thermal stability independently of their base

instant case, Schwartz et al. suggests the use of methylphosphonate as an alternative to the natural phosphodiester backbone that links nucleosides.

Thus, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to modify the backbone of at least one X1-X4 of Nguyen et al. to render it as a nucleoside methylphosphonate. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to stabilize the oligonucleotide. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the substitution of one nucleoside linkage for another is routinely practiced in the art.

It is recognized that Nguyen et al. does not comment on the immunostimulatory activity of the oligonucleotide compounds that Nguyen et al. teaches, however, MPEP § 2112 [R3] sets forth that something which is old does not become patentable upon the discovery of a new property. Specifically, MPEP § 2112 [R3] [I] states: "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)". Hence, Applicant's discovery of a previously unappreciated property, the immunostimulatory property of the oligonucleotide compounds of Nguyen et al., of

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content for DNA sequencing by hybridization. Nucleic Acids Research, 1997, Vol. 25, No. 15, 3059-3065.

the prior art composition does not render the old composition patentably new to the Applicant.

5. Claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao et al.[4], in view of Schwartz et al.

In response to the rejection, Applicant submits the same arguments as those addressed in paragraph No. 4 of the instant application. These arguments have been considered and found not persuasive for the reason(s) set forth in the cited paragraph.

Zhao et al. teaches of immunostimulatory oligonucleotides having the formula X1X2CGX3X4, wherein X1-X4 are a nucleoside each; and wherein C is 2'-deoxycytidine and G is 2'-deoxyguanosine.

Zhao et al. does not teach the use of a non-natural pyrimidine nucleoside for C.

However, at the time the invention was made, Schwartz et al. suggest the use cytosine arabinoside, a non-natural pyrimidine as an alternative to natural pyrimidine. [Claim 4, page 39 in particular.] Cytosine arabinoside is in accordance with formula (I).

Hence, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to use cytosine arabinoside as an alternative to the natural pyrimidine present in the oligonucleotides of Zhao et al. One of ordinary skill in the art, at the time the invention was made would have been motivated to do so to make an immunostimulatory oligonucleotide. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the substitution of equivalents is routinely practiced in the art.

Regarding the limitation that at least one of X1-X4 is an immunostimulatory moiety instead of being a nucleoside each, wherein the immunostimulatory moiety is defined is a nucleoside methylphosphonate, it is noted that Schwartz et al. teaches that the nucleosides present in immunostimulatory oligonucleotides may comprise a modified backbone, Wherein instead of the naturally occurring phosphodiester backbone that allows linkage between nucleosides can be substituted with other phosphorous backbone derivatives to increase the stability of the oligonucleotide. Of the derivatives that Schwartz et al. teach include alkylphoshate or the like, which methylphosphate is the most basic alkylphosphate. Addition to suggesting alkylphosphate, Schwartz et al. also referred to the teachings of Peyrottes et al., which teaches the use of methylphosphonate to stabilize oligonucleotides. Hence, in the instant case, Schwartz et al. suggests the use of methylphosphonate as an alternative to the natural phosphodiester backbone that links nucleosides.

Thus, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to modify the backbone of at least one X1-X4 of Zhao et al. to render it as a nucleoside methylphosphonate. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to stabilize the oligonucleotide. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the substitution of one nucleoside linkage for another is routinely practiced in the art.

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[4] Zhao et al. Immunostimulatory activity of CpG containing phosphorothioate oligodeoxynucleotide is modulated b modification of a single deoxynucleoside. Bioorganic and Medicinal Chemistry Letters, May 15, 2000, Vol. 10, 1051-1054.

6. Claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al.,[5] in view of Schwartz et al.

In response to the rejection, Applicant submits the same arguments as those addressed in paragraph No. 4 of the instant application. These arguments have been considered and found not persuasive for the reason(s) set forth in the cited paragraph.

Agrawal et al. teaches of immunostimulatory oligonucleotides having the formula X1X2CGX3X4, wherein X1-X4 are a nucleoside each; and wherein G is 2'deoxyguanosine. [See Figure 2, in particular.]

Agrawal et al. does not teach the use of a non-natural pyrimidine nucleoside for C.

However, at the time the invention was made, Schwartz et al. suggest the use cytosine arabinoside, a non-natural pyrimidine as an alternative to natural pyrimidine. [Claim 4, page 39 in particular.] Cytosine arabinoside is in accordance with formula (I).

Hence, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to use cytosine arabinoside as an alternative to the natural pyrimidine present in the oligonucleotides of Agrawal et al. One of ordinary skill in the art, at the time the invention was made would have been motivated to do so to make an immunostimulatory oligonucleotide. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the substitution of equivalents is routinely practiced in the art.

[5] Agrawal et al. U.S. Provisional Application No. 60/178562, which U.S. Patent No. 6815429 has priority.

Regarding the limitation that at least one of X1-X4 is an immunostimulatory moiety instead of being a nucleoside each, wherein the immunostimulatory moiety is defined is a nucleoside methylphosphonate, it is noted that Schwartz et al. teaches that the nucleosides present in immunostimulatory oligonucleotides may comprise a modified backbone, Wherein instead of the naturally occurring phosphodiester backbone that allows linkage between nucleosides can be substituted with other phosphorous backbone derivatives to increase the stability of the oligonucleotide. Of the derivatives that Schwartz et al. teach include alkylphoshate or the like, which methylphosphate is the most basic alkylphosphate. Addition to suggesting alkylphosphate, Schwartz et al. also referred to the teachings of Peyrottes et al., which teaches the use of methylphosphonate to stabilize oligonucleotides. Hence, in the instant case, Schwartz et al. suggests the use of methylphosphonate as an alternative to the natural phosphodiester backbone that links nucleosides.

Thus, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to modify the backbone of at least one X1-X4 of Agrawal et al. to render it as a nucleoside methylphosphonate. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to stabilize the oligonucleotide. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the substitution of one nucleoside linkage for another is routinely practiced in the art.

Conclusion

7. No claims are allowed.

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY M. LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EMILY M LE/
Primary Examiner, Art Unit 1648

/E. M. L./